Debates in Pregnancy Related GN

AMIR EL OKELY
MRCP, MD

Agenda

- *Renal biopsy in pregnancy*
- *Immunosuppressive drugs in pregnancy*
- *Termination of pregnancy*

- The combination of kidney disease and pregnancy has long been recognized as a high-risk situation.
- When renal disease occur first time during pregnancy, it presents unique problems for both the obstetric and renal teams.
- Particularly difficult can be distinguishing preeclampsia from preexisting kidney disease.
- Decision-making regarding kidney biopsy and treatment of GN during pregnancy is often much more complicated by safety concerns for both the mother and fetus.

Clin J Am Soc Nephrol 8: 1027–1033, 2013

Proteinuria in pregnancy

Differential Diagnosis:

- Primary renal disease
- Systemic disease
- Preeclampsia

Considerations:

- Timing
- was renal disease known prior to conception
- If no preexisting conditions, then did proteinuria began before or after 20th week of pregnancy

Examples of some renal diseases encountered in pregnancy

Glomerular
Primary renal
Minimal change disease
Glomerulonephritis
Membranous nephropathy
Chronic glomerulosclerosis
IgA nephropathy
Interstitial
Interstitial nephritis
Polycystic kidney disease
Systemic
Glomerular
Diabetes mellitus
Systemic lupus erythematosis
Systemic vasculitis
Hypertensive nephrosclerosis
Reflux nephritis
Obstruction
Congenital anomalies
Multiple myeloma
Infection (eg, HIV, hepatitis B/C)

Table 1. Differentiation of pre-eclampsia, HELLP syndrome, and active lupus nephritis

	Pre-Eclampsia	HELLP Syndrome	Active Lupus Nephritis
Timing in pregnancy	After 20 wk of gestation	After 20 wk of gestation	All gestational ages
Complement (C3, C4)	Normal	Normal	Typically decreased
Thrombocytopenia	Absent	Present	Present
Neutropenia	Absent	Absent	Present
Active urine sediment	Absent	Absent	Present (may be benign in membranous lupus nephritis)
Other organ involvement	Absent	Absent	Present
Anti-double-stranded DNA antibodies	Absent	Absent	Present
Anti-C1q antibodies	Normal	Normal	May be high
Abnormal liver function tests	Absent	Present	Absent
Serum uric acid	Increased	Increased	Normal (may be elevated with reduced GFR)
Hypertension (BP >140/90 mmHg)	Present	Absent in 10%–15%	Variable
Elevation in creatinine (>1.2 mg/dl)	Typically absent	May occur in up to 10%	Commonly present

HELLP, hemolysis, elevated liver enzymes, low platelet count.

Kidney Biopsy in Pregnancy

The role of renal biopsy in women with kidney disease identified in pregnancy

- In some situations, it may be important to know the exact etiology of the renal disorder in order that immediate disease-modifying treatment can be commenced to enable the pregnancy to reach viability.
- However, in other circumstances, such as the detection of non-nephrotic range proteinuria in the absence of features of a systemic disease process, definitive diagnosis of renal disease can be delayed until post-partum.

The role of renal biopsy in women with kidney disease identified in pregnancy

- Renal biopsy has been performed during pregnancy since its introduction in the 1960s.
- Initial series showed a high incidence of complications but subsequent reports indicate a complication rate similar to non-pregnant women.
- Although it has been established that there is no greater risk of complications of renal biopsy in pregnancy, the consequences to the mother and fetus of post-biopsy hemorrhage could be severe.
- There is no standard of practice.

There are three widely accepted indications for kidney biopsy during pregnancy.

- First, new-onset LN biopsy because diffuse proliferative LN must be treated immediately with immunosupressive drugs.
- Any unexplained deterioration of kidney function is a second indication for renal biopsy.
- The third indication for biopsy during pregnancy is massive proteinuria

Acute Glomerulonephritis in Pregnancy*

V. K. KNUTZEN, M.B. CH.B. UNIV. CAPE TOWN, M.R.C.O.G., *Department of Obstetrics and Gynaecology* AND G. N. THATCHER, M.B. CH.B. UNIV. CAPE TOWN, F.C.P.(S.A.), *Renal Service, Groote Schuur Hospital and Department of Medicine, University of Cape Town*

TABLE I. SOME FEATURES OF ACUTE GLOMERULONEPHRITIS AND COURSE OF PREGNANCY

	Case 1	Case 2	Case 3	Case 4
Age (yrs)	35	28	23	35
Race	White	Coloured	Bantu	Coloured
Parity	3	4	1	2
Duration of pregnancy at onset	7 weeks	28 weeks	10 weeks	12 weeks
Preceding infection	Sore throat	Cholecystectomy —wound sepsis	Upper resp. tract	None
Organism isolated	None	β-haemolytic streptococcus	β-haemolytic streptococcus	None
ASO titre (Todd units)	200	50	500	500
Complement	Reduced	Reduced	Not done	Normal
Renal biopsy	Not done	Active GN*	Not done	RPGN†
Outcome of nephritis	Recovered	Recovered	Persistent (?)	Progressive
Duration of pregnancy at termination	38 weeks	31 weeks	40 weeks	21 weeks
Method of termination	Induction	Induction	Spontaneous labour	Hysterotomy
Weight of infant	2,95 kg	1,7 kg	2,7 kg	Not weighed
Outcome for infant	Alive	Alive— neonatal death	Alive	Abortion

* Active proliferative glomerulonephritis.
† Rapidly progressive proliferative glomerulonephritis.

SUMMARY

Four cases of acute glomerulonephritis in pregnancy are described. The pattern of the disease followed that seen in the non-pregnant adult. No adverse effect on the foetus was detected. Renal function, as measured by serum creatinine levels and endogenous creatinine clearance, was the only indication used for termination of pregnancy. Renal biopsy performed in 2 cases was of value in confirming the diagnosis and assessing the severity of the nephritis. Superadded urinary tract infection occurred in all patients and contributed significantly to the morbidity.

S. Afr. J. Obstet. Gynaec., **11**, 24 (1973).

Nephrol Dial Transplant (2008) 23: 201–206
doi:10.1093/ndt/gfm572
Advance Access publication 25 August 2007

NDT
Nephrology Dialysis Transplantation

Original Article

The role of renal biopsy in women with kidney disease identified in pregnancy

Clara Day[1], Peter Hewins[1], Sarah Hildebrand[1], Lumaan Sheikh[2], Gabrielle Taylor[1], Mark Kilby[2] and Graham Lipkin[1]

[1]Dept of Nephrology, University Hospital, Birmingham NHS Foundation Trust, Edgbaston, Birmingham B15 2TH and [2]Dept of Fetal Medicine, Birmingham Women's Health Care NHS Trust, Birmingham, B15 2TG

- 20 women presenting with renal disease of a severity to warrant renal biopsy during pregnancy were compared to 75 women who had an initial presentation of renal disease in pregnancy and underwent post-partum renal biopsy.

Indication for biopsy

- Four patients had a previous diagnosis of lupus nephritis with a deterioration of renal parameters during pregnancy,
- Four presented for the first time with proteinuria and positive autoimmune serology during pregnancy,
- Four presented with first onset of nephrotic syndrome
- Three were biopsied in the first trimester with proteinuria and impaired renal function to assess degree of renal damage
- Five were biopsied in the second trimester with worsening proteinuria and hypertension.

Complication of biopsy

- One patient had minor post-biopsy haematuria which settled spontaneously.

- Nine of the 20 patients had an immediate change in therapy (mainly the initiation or increase in dose of immunosuppressive medication) as a consequence of knowledge of renal histology.

Table 1. Clinical features of women biopsied in pregnancy

	Age	Gestation (weeks)	Creatinine (μmol/l)	Albumin g/24 h	Immunology	Biopsy diagnosis
1	20	27	74	2.9	Negative	FSGS
2	32	16	99	0.2	ANA+	Granulomatous interstitial nephritis
3	31	17	321	12.5	ANA1:400	Active lupus nephritis
4	28	20	300		dsDNA+	Active lupus nephritis
5	29	31		Nephrotic	negative	Lupus nephritis
6	24	21	94	1.4	Negative	FSGS
7	29	6		Nephrotic	n/a	Minimal change nephropathy and acute tubular necrosis
8	26	13			n/a	Membranoproliferative gn and dense deposit disease
9	17	25	68	10.2	ANA1:1600 dsDNA152	Lupus nephritis
10	22	30	70	7.1	ANA1:1600 dsDNA337	Lupus nephritis
11	19	8	81	Nephrotic	n/a	Familial non-IgA mesangioproliferative GN
12	24	23	78	2.7	Negative	FSGS
13	39	31	55	0.9	Negative	FSGS
14	37	24	80	7.3	ANA+C4low	FSGS
15	31	27	56	9	ANA+dsDNA +SSA+	Lupus nephritis
16	37	9	160	0.6	ANCA 1:25	Membranoproliferative GN sec to SCD
17	22	7	47	1.2	dsDNA127	Lupus nephritis
18	21	8	73	6	ACAIgM 23	Sickle cell nephropathy
19	35	14	174	4	Negative	Henoch Schonlein nephritis with severe chronic damage
20	39	26	86	1.8	Negative	IgA nephropathy

ANA, anti-nuclear antibodies; dsDNA, anti double-stranded DNA antibodies; ACAIgM, anti-cardiolipin antibodies (IgM); FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis.

Table 2. Results at follow-up [median 103.3 months (2.5–256)] for patients biopsied during pregnancy

CKD category	*N* (total 20)	Albumin excretion g/24 h	*N* (total 20)
1	5 (25%)	<0.3 g	6 (30%)
2	6 (30%)	0.3–2 g	5 (25%)
3	2 (10%)	>2 g	2 (10%)
4	0	ESRF	6 (30%)
5	7 (35%) [six ESRF (30%)]	No data	1 (5%)

Post- pregnancy biopsies

Seventy-five women underwent renal biopsy following pregnancy with abnormal renal parameters diagnosed either during pregnancy or immediately post-partum.

- Median age at biopsy was 31 years(15–55).
- Only those with acute renal failure were biopsied immediately post-partum.
- In those with persistent proteinuria renal biopsy was generally delayed at least 6 months

Clinical presentation

- Fifty (83%) of the women presented with proteinuria in pregnancy
- In 23 cases this was associated with superimposed pre-eclampsia with proteinuria persisting for several months post-partum
- Twenty-seven women presented with newly diagnosed proteinuria in the absence of pre-eclampsia
- Six women presented with nephrotic syndrome
- Six with newly diagnosed renal impairment
- Four with isolated haematuria
- Three with acute renal failure.

Table 3. Biopsy diagnosis of women diagnosed post-partum ($n = 75$)

Biopsy diagnosis	n	
Thin glomerular basement membrane disease	9	
Primary glomerular disorder (not lupus)	42	21 FSGS 10 IgA nephropathy 6 mesangio-proliferative non-IgA glomerulonephritis 2 chronic glomerular disease 1 minimal change nephropathy 1 glomerular dense deposit disease 1 membranous nephropathy
Lupus nephritis	6	
Other	16	3 late non-glomerular disease 2 presumed hypertensive damage 1 chronic pyelonephritis 1 sickle cell nephropathy 2 late effects of pre-eclampsia 2 diabetic nephropathy 1 tuberculosis 1 Alport's disease 1 renal transplant cortical necrosis 1 haemolytic uraemic syndrome 1 acute tubular necrosis secondary to HELLP syndrome
Normal (on light microscopy)	2	

Outcome by category

The worst outcome occurs in those with:

- Interstitial non-glomerular disease with four of five being classified as CKD 3–5.
- Those reaching ESRF had diagnoses of
  - ◊ acute cortical necrosis following ante-partum hemorrhage
  - ◊ intra-uterine death
  - ◊ late tubulo-interstitial damage
  - ◊ late FSGS
  - ◊ renal TB
  - ◊ sickle cell nephropathy
  - ◊ glomerular dense deposit disease
  - ◊ lupus nephritis

DOI: 10.1111/1471-0528.12111
www.bjog.org

Systematic review

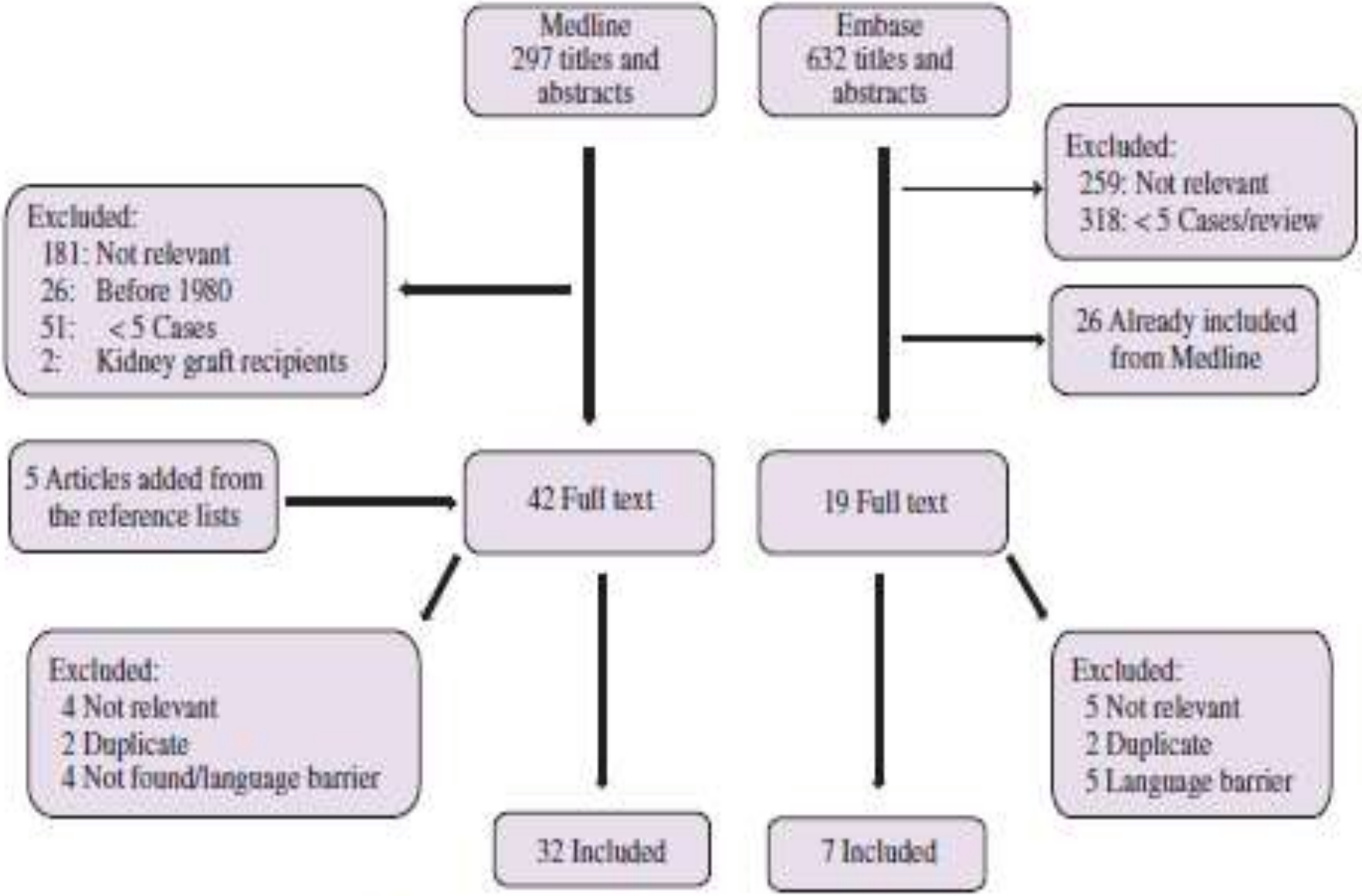
Kidney biopsy in pregnancy: evidence for counselling? A systematic narrative review

GB Piccoli,[a] G Daidola,[a] R Attini,[b] S Parisi,[b] F Fassio,[b] C Naretto,[c] MC Deagostini,[a] N Castelluccia,[a] M Ferraresi,[a] D Roccatello,[c] T Todros[b]

[a] Struttura Semplice of Nephrology, Department of Clinical and Biological Sciences, University of Torino, [b] Mauriziano Postal Unit, Department of Obstetrics and Gynecology, [c] Interregional Center for rare diseases, Department of Clinical and Biological Sciences, University of Torino, Orbassano, Torino, Italy

Correspondence: Dr GB Piccoli, Struttura Semplice of Nephrology, Department of Clinical and Biological Sciences, University of San Luigi Gonzaga, Regione Gonzole 10, 10043 Orbassano, Torino, Italy. Email gbpiccoli@yahoo.it or giorgina.piccoli@unito.it

Accepted 1 October 2012. *Published Online* 15 January 2013.



China: 17 papers, 3 already included from Medline, 14 not relevant or case reports;

Cochrane: 3 papers, 1 already included from Medline, 2 not relevant.

Table 2. Indications for kidney biopsy and timing of the biopsy

First author	Indications for kidney biopsy—inclusion criteria	Timing of the kidney biopsy
Kidney biopsy in pregnancy only		
Zineb	Nephrotic syndrome in seven women; macroscopic haematuria and hypertension in one each	Gestational age 13 ± 5 weeks
Wide-Swensson	I: Pregnancy-induced Ht; mild PE; severe PE (proteinuria > 3000 mg/l); II: nonproteinuric Ht; III: control: 18 healthy pregnancies	Gestational age: I: 33.8; II: 34.7; III: 35.2 weeks
Chen	Undiagnosed renal disease during pregnancy (proteinuria, haematuria, hypertension or azotaemia).	Gestational age: 22.3 (20–25) weeks
Weiner	Severe PE < 34 weeks in women planning future pregnancy, if delivery by caesarean section is necessary	At caesarean delivery: 30 (24–36) weeks
Packham	Impaired renal function, nephrotic syndrome, haematuria, proteinuria or Ht	Gestational age: 15 (4–28) weeks

Kidney biopsy during pregnancy and/or within 2 months of delivery

Day	I: In pregnancy: decrease of renal function, proteinuria, autoimmune serology, worsening proteinuria or Ht; II: postpartum: proteinuria, haematuria or AKI	I: Gestational age 20.5 weeks; II: AKI: postpartum; otherwise ≥ 6 months
Kuller	I: In pregnancy: to differentiate between PE and other renal diseases; II: postpartum: worsening kidney disease or Ht	I: Gestational age: 25 (11–30) weeks; II: postpartum: 5 (4–19) days
Stettler	Nondiabetic proteinuria ≥ 500 mg/day, no known renal disease, no reversible dysfunction or PE	In pregnancy: gestational age 16 weeks; postpartum: NR
Hill	PE in the absence of other kidney disease	Intrapartum: 28 (18–33) weeks; postpartum: 4–10 days
Packham	PE: hypertension and proteinuria in pregnancy, which resolved in the early postpartum period. I: in pregnancy; II: post partum	I: Gestational age: 28 (20–34) weeks; II: postpartum: 4 (3–9) days
Sommers	Clinical toxaemia of pregnancy	Mid-pregnancy, near term and postpartum

Conclusions

The evidence regarding the pros and cons of kidney biopsy in pregnancy was found to be heterogeneous; however, the risks of complications were higher in pregnancy than in the postpartum period (7% versus 1%, respectively).

Our review suggests that the procedure should be limited to women with a suspicion of glomerular disease severe enough to warrant immediate treatment. The risks and advantages of empirical therapeutic approaches have also to be considered in each case. As evidence is still scant, we should also inform women about the limits of the present knowledge, emphasising that, although the first kidney biopsies in pregnancy were carried out in the late 1950s, the treatment of a pregnant woman with proteinuria suspected to have a cause other than PE is still based on sporadic and, to some extent, experimental experiences.

IMMUNOSUPPRESSIVE DRUGS IN PREGNANCY

Pregnancy safety categories

Category A

Adequate human studies failed to demonstrate a risk to the fetus

Category B

Animal studies show no risk to the fetus and no adequate studies in pregnant women OR animal studies have shown an adverse effect, but studies in pregnant women failed to demonstrate a risk to the fetus

Category C

Animal studies show adverse effect to fetus and no adequate studies in humans, BUT potential benefits may outweigh potential risks

Category D

Evidence of human fetal risk but potential benefits may warrant use of the drug despite potential risks.

Category X

Studies in animals or humans have demonstrated fetal abnormalities and/or there is evidence of fetal risk, and the risks clearly outweigh potential benefits

Prednisone (category c)

Maternal effects

Associated with premature rupture of membranes

Crosses placenta

10:1 ratio

Prenatal exposure

Fetal growth restriction

Low birth weight

Safe in breastfeeding

Azathioprine (category d)

Crosses placenta

Prenatal exposure

Protected from toxicity 2' lack of enzyme to convert to active form

Growth restriction

Myelosuppression

Leukopenia avoided if maternal WBC ≤ 7500

Fetal malformations (4-9%)

3-5% seen in gen pop

No known associated congenital malformation

Avoid breastfeeding

Mycophenolic acid products (category d)

Prenatal exposure

>20% risk of congenital malformation

Unknown safety in breastfeeding

Stop drug > 6 wks prior to conception and throughout pregnancy

Sirolimus (category c)

Maternal effects

May inhibit myometrial hyperplasia required in early gestation

Paternal effects

Decreased fertility in men

Prenatal exposure

Decreased fetal weight

Delayed skeletal ossification

Unknown safety with breastfeeding

Cyclosporine (category c)

Maternal effects

Increased metabolism in pregnancy

Requires higher doses

Crosses placenta

30-60% of what is in maternal blood

Prenatal exposure

Growth restriction

Premature birth

Low birth weight

Avoid breast feeding

Tacrolimus (category c)

Maternal effects
Possible miscarriage
Frequent monitoring drug levels (q 2-4 wks)

Crosses placenta

Prenatal exposure
Transient perinatal hyperkalemia
Increased incidence of diabetes

Avoid breastfeeding

Rituximab (category c)

- Rituximab is a human/murine chimeric monoclonal IgG directed against the CD20 protein on B lymphocytes.
- The drug may persist in the maternal circulation, has been reported to cause hematologic abnormalities, and predisposes to infections .
- Women are advise not to conceive for a year after receiving rituximab.

Table 2. Anti-inflammatory and immunosuppressive drugs in pregnancy

Drug Name	Comments	FDA Class[a]	Breastfeeding[b]
Corticosteroids	Risks of use often outweighed by risk of underlying disease. Potential risks for orofacial clefts (3 of 1000 births) and premature birth	C	Usually compatible
Hydroxychloroquine	Considered safe in pregnancy at 200–400 mg/d. Discontinuation during pregnancy associated with increased risk of lupus flare. May use for maintenance or mild flares	Not assigned	Usually compatible
NSAID	Avoidance after 28 weeks of gestation because of the effects of NSAID-related prostaglandin inhibition on the fetal cardiovascular system (closure of ductus arteriosus)	C	Usually compatible
Cyclosporine	Can be maintained in pregnancy at lowest effective dose. No significant increase in rate of congenital malformations	C	Not recommended
Tacrolimus	Can be maintained in pregnancy at lowest effective dose. Potential risks of neonatal hyperkalemia and renal dysfunction	C	Not recommended
Rituximab	Limited safety data. May alter fetal and neonatal B cell development	C	Not recommended
IVIG (γ globulin)	Data are lacking, but may be helpful for lupus nephritis flare refractory to medical therapy	C	Compatible
Azathioprine	May use for flare during pregnancy. Consider as alternative to mycophenolate. Avoid doses >1.5–2 mg/kg per day due to risk of suppressed neonatal hematopoiesis	D	Not recommended
Mycophenolate mofetil	Contraindicated during pregnancy due to teratogenicity	D	Not recommended
Cyclophosphamide	Useful when maternal disease is life threatening. High risk of fetal loss, but less pronounced in more recent studies	D	Not recommended
Methotrexate	High risk of miscarriage and congenital abnormality. Treatment should be withdrawn 3 months before pregnancy	X	Not recommended

A Systematic Review and Meta-Analysis of Pregnancy Outcomes in Patients with Systemic Lupus Erythematosus and Lupus Nephritis

Andrew Smyth,* Guilherme H.M. Oliveira,† Brian D. Lahr,‡ Kent R. Bailey,‡ Suzanne M. Norby,§‖ and Vesna D. Garovic§‖

*Department of Medicine, National University of Ireland, Galway, Ireland; §Department of Medicine, ‡Division of Biomedical Statistics and Informatics, and ‖Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota; and †Department of Cardiology, University of Texas M. D. Anderson Cancer Center, Houston, Texas

Conclusions

Our meta-analysis of 2751 pregnancies in patients with SLE showed lupus nephritis to be associated with premature birth and hypertension during pregnancy. In addition, positive APAs were associated with an increased risk for hypertension in these patients. Of note, hypertensive pregnancy disorders are increasingly recognized as risk factors for future cardiovascular disease, which is a leading cause of morbidity and mortality in SLE patients (49). Therefore, optimal timing of pregnancy in SLE patients with lupus nephritis may both decrease hypertensive pregnancy events and have a long-term impact on cardiovascular events later in life.

Our data further support the importance of pre-pregnancy counseling of women with SLE and lupus nephritis with respect to optimal timing of pregnancy relative to disease activity. It also emphasizes the importance of screening for APAs in these patients. Because much of the evidence is derived from studies focused on different outcomes, heterogeneous study designs, and defined endpoints, our study highlights the need for prospective studies with well-defined SLE activity and pregnancy outcomes.

Table 3. Laboratory testing of SLE/lupus nephritis patients during pregnancy

Timing	Suggested Laboratory Tests	Comments
Preconception counseling and/or first prenatal visit	Urinalysis Determination of proteinuria	Obtain protein/creatinine ratio, optimally 24-hour urine protein
	Complete blood count Serum creatinine Antiphospholipid antibodies Anti-SSA/Ro and anti-SSB/La antibodies	If positive, conduct weekly fetal heart rate assessments from 16 to 24 weeks of gestation and every other week thereafter until 32 weeks
	Anti-double-stranded DNA antibody Complement studies Liver function tests	
Every month	Urinalysis Determination of proteinuria Serum creatinine	If these test results are abnormal, obtain lupus serologies and complement studies; consider a renal biopsy before 32 weeks of gestation
Every trimester[a]	Complete blood count Anti-double-stranded DNA antibody Complement studies Liver function tests (for patients taking azathioprine)	

Termination of pregnancy

Indication for termination of pregnancy

- Inability to control blood pressure.
- Deteriorating GFR without reversible component
- Neurological abnormalities
- Elevated transaminases
- Failure of fetal growth
- Worsening thrombocytopenia

THANK YOU